URTICARIA TREATED WITH EPINEPHRIN.

By Arthur W. Swann, M.D.,

ASSISTANT VISITING PHYSICIAN TO THE SECOND MEDICAL DIVISION OF THE PRESBYTERIAN HOSPITAL, NEW YORK; INSTRUCTOR IN MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

In six cases of urticaria which I have treated by the subcutaneous administration of epinephrin the injections were followed by a rapid disappearance of the erythema and wheals.[1] In each case a dose corresponding to about eight minims for an adult of one hundred and forty pounds was given hypodermically, and the dose was repeated in ten minutes. Two doses sufficed in every instance to cause the complete fading of the rash. An improvement was usually evident eight minutes after the initial dose, and was most marked between ten and twenty minutes, during which time, especially in the severe cases, the rapidity with which the eruption subsided was very striking. After twenty minutes there usually remained some erythematous blotches, or small, pale wheals, which continued to fade until the skin looked entirely normal. All itching ceased in from five to twenty minutes after the first dose.

In Case V the eruption did not return until three days later, when epinephrin was again given (see Case VI). In Case II it recurred after seven hours. In the three most severe cases (Cases III, IV, and VI), all of which were serum rashes, the wheals began to reappear in from one to two and a half hours after the initial dose of epinephrin, and increased steadily for from one to three hours more, when the eruption was again at its height. I have no record of Case I, and cannot say whether or not the wheals recurred.

Unfortunately I was not able to be with any of the patients when the rash began to reappear, and therefore had no opportunity of repeating the treatment in such cases. There is no doubt that if the exciting cause of the urticaria is still sufficiently active the wheals will recur in an hour or two unless the treatment is continued. It will be interesting to see whether or not the condition can be relieved for longer periods, or even permanently, by repeated and properly regulated doses.

A brief account of each case follows. For blood pressure curves, see chart, page 376.

Case I.—Boy, aged about twelve years, who while a hospital patient incidentally developed moderate urticaria, supposed to be of gastro-intestinal origin. He was given two subcutaneous injections of adrenalin ten minutes apart. The wheals started to fade soon after the first injection, and rapidly disappeared after the second. I have no records of this case, and cannot say whether or not the wheals returned.

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[1] The preparation used was the 1 to 1000 adrenalin chloride solution of Parke, Davis & Co.

CASE II.—Man, aged twenty-eight years, who for some time had had two or three attacks every year of swelling and redness of the fingers and toes, generally but not always associated with urticaria. When seen by me he had many small wheals and irregular red blotches on the dorsum of both hands and wrists, and complained of a disagreeable sensation of swollen feet, which on walking were somewhat painful, and made him feel as if his shoes were full of cotton. The systolic blood pressure was 113 mm. He was given eight minims of adrenalin solution subcutaneously, and the dose was repeated in ten minutes. Eight minutes after the first dose the subjective sensations in his feet were less marked, and the wheals and blotches on both hands and wrists were fading. In twenty minutes only a few faint red blotches on his left hand remained, and one foot felt slightly swollen. In thirty-two minutes no trace of the eruption remained and both feet felt entirely normal. The patient remained well for seven hours, when the condition returned less severely than before.

CASE III. (Diphtheria).—Boy, aged three and a half years. Weight about thirty-five pounds. Systolic blood pressure, 75 mm. The patient had received a single dose of antitoxin eight days before. At this time his abdomen and the inner sides of both thighs were covered with large wheals, around which was a fiery red erythema. Wheals and red blotches were scattered irregularly over his face and both arms, and there was some edema of the foreskin. The eruption was a severe one, and the itching was extreme.. Two minims of adrenalin solution were given subcutaneously, and repeated in ten minutes. In six minutes after the first dose there was a slight diminution of the erythema on his abdomen. In eight minutes a change on his abdomen, face, and thighs was perfectly distinct. In twelve minutes the erythema was nearly gone. The wheals then began to disappear with great rapidity, and in nineteen minutes had entirely faded from the face, abdomen, and right arm, a few still remaining on the left hand and thighs. These continued to fade, and in twenty-eight minutes had disappeared from his hand and right thigh, leaving only a few small whitish elevations on the inner side of the left thigh, which failed to entirely disappear. The edema of the foreskin was also gone. The boy was much relieved for the time being, and for the first time that day went to sleep. One hour and ten minutes after the first dose the wheals began to reappear, and three hours later were as bad as ever.

CASE IV. (Convalescent Diphtheria).— Boy, aged ten years. Weight about seventy pounds. Systolic blood pressure, 80 mm. 10,000 units of antitoxin had been given eight days before. Again in this case the urticaria was severe, wheals and erythema being profusely scattered over the face, neck, calves, and arms. There were a few wheals on the abdomen, and the penis was swollen on one side. He was given four minims of adrenalin solution, and after ten minutes, five minims. Nine minutes after the initial dose there was slight fading on his neck, back, and right calf. Though the eruption was still very marked, the boy said there was no longer any itching. In fifteen minutes the eruption was rapidly fading, and in nineteen minutes was almost gone from the face, neck, and back. In twenty-five minutes the wheals were entirely gone, and all that remained of the eruption was a blotchy erythema, which still persisted on the right arm and both calves. These spots continued to fade, and in thirty-five minutes the skin was entirely clear. In two hours and a half after the first dose of adrenalin the wheals were again appearing, and soon after the eruption was as profuse as ever.

Case V. (Diphtheria).—Boy, aged seven years. Weight about sixty pounds. Blood pressure, 80 mm. The patient had received 10,000 units of antitoxin, and had developed the eruption three hours later. When I saw him, one hour after the first appearance of the rash, there were a few single wheals on the left hip, face, shoulder, and pubis. The right cheek was swollen and blotchy. The rash was of a mild type. Four minims of adrenalin solution were given, and the dose repeated in fifteen minutes. In four minutes the wheal on his hip was distinctly blanched. In eight minutes all the wheals had faded somewhat. In sixteen minutes they were nearly gone. In twenty-five minutes they had entirely disappeared. The eruption did not return for three days, when it recurred in severer form, and the patient was again treated with epinephrin as Case VI. It is interesting to note that in this case the blood pressure failed to rise more than 2 mm., and yet the wheals were affected as in the other cases.

Case VI.—Same boy as Case V, three days later. The eruption was much more extensive this time, the wheals covering in a solid mass the inner sides of both thighs, and being scattered over the face, back, and chest. The systolic blood pressure was now 68 mm. He was given four minims of adrenalin solution, and the dose was repeated in ten minutes. Slight fading was noticeable ten minutes after the initial dose. In nineteen minutes the face and back were entirely clear, the chest nearly so, and the thighs much improved. In thirty-five minutes the eruption had entirely vanished, except for a few small whitish elevations on the inner side of the left thigh, resembling those in Case III. These continued to fade, and fifteen minutes later were entirely gone. In two hours after the intitial dose a few large wheals began to reappear on the back, and an hour and a quarter later the eruption was again at its height.

The striking manner in which the erythema and wheals have subsided in these cases is interesting in connection with work recently done on epinephrin by Janeway and Park.[2] Using strips of excised peripheral arteries they confirmed the work of Meyer[3] and others, which showed that contraction occurred when subjected to epinephrin in high dilutions, and they showed further that the degree of contraction depended not only on the strength of epinephrin, but also on the state of tonus in which the vessels were at the time. That is, if the vessels were already somewhat contracted, little further contraction resulted from the epinephrin; whereas, if they were relaxed, the contraction was much greater. Park[4] found that the same principle held good in regard to the dilatation of the coronary artery of the ox, which is produced by epinephrin, and that if the artery were contracted

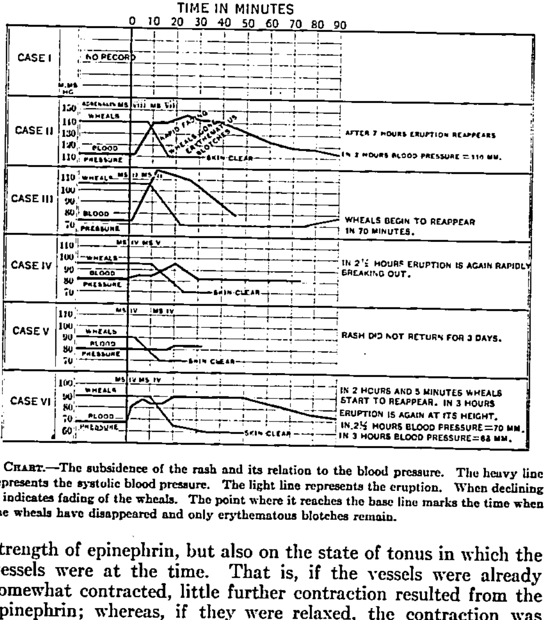

CHART.—The subsidence of the rash and its relation to the blood pressure. The heavy line represents the systolic blood pressure. The light line represents the eruption. When declining it indicates fading of the wheals. The point where it reaches the base line marks the time when the wheals have disappeared and only erythematous blotches remain.

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[2] The Question of Epinephrin in the Circulation and its Relation to Blood Pressure, Jour. Exper. Med., 1912, xvi, 541.

[3] Ueber einige Eigenschaften der Gefässmuskulatur mit besonderer Berücksichtigung der Adrenalinwirkung, Zeitschr. f. Biol., 1906, xlviii, 352.

[4] Observations with Regard to the Action of Epinephrin on the Coronary Artery, Jour. Exper. Med., 1912, xvi, 532.

a much greater dilatation occurred than if it were already in a state of relaxation. He suggested that this might explain the striking relief often produced by epinephrin in cases of bronchial asthma, where the effect on the bronchi is out of all proportion to any apparent effect elsewhere in the body; for as has been observed by Eppinger and Hess,[5] and also by Frank[6] there may result marked relaxation of the bronchi, with little or no rise in blood pressure. In such cases as Park[7] pointed out, the drug seems to have a more or less selective action on certain structures, depending probably upon their state of tonus.

From the results obtained in these six cases of urticaria, it seems probable that in such cases too the vessels in the wheals are in a state of optimal tonus for the action of epinephrin, and that on them the drug has an unusual and selective effect. In contrast to asthma, however, the rise of blood pressure which occurred was in most cases greater than usually follows subcutaneous injections of epinephrin in other types of disease, or in health, and may have been due to a generally relaxed condition of the arterial tree, which one would expect to be present in such cases. A relationship between the rise in pressure and the subsidence of the eruption is shown in the chart, where it is readily seen that in every instance except in Case V the wheals began to fade soon after a marked rise in pressure had occurred, and continued to fade while the pressure was rising or still above normal. On the other hand, the inconstancy of this relationship is shown in Case V, where the rash nearly disappeared before any rise of blood pressure took place, and by the fact that in most of the cases the wheals did not reappear for some time after the pressure had again fallen to its starting point. It is therefore by no means certain whether the disappearance of the rash depends entirely upon the local contraction of the bloodvessels or whether it also depends in part upon some other process. Meltzer and Auer[8] have shown by animal experimentation that epinephrin retards absorption from the tissues into the blood and transudation from the blood into the tissues, and that this effect is maintained well after the blood pressure has fallen to normal. It is possible that this may be instrumental in causing the wheals to disappear, though it would seem more logically to be a factor in preventing their reappearance.

The effect produced in these cases of urticaria suggests that epinephrin might be used to advantage in certain more serious yet similar conditions. One such condition is "angioneurotic edema" in its various forms. At the present time, except for general hygienic management, little can be done for these cases, and it will be interesting to see what can be accomplished with repeated doses of epinephrin. In cases of edema of the epiglottis or larynx due to disturbance of this type epinephrin given intravenously, if its action were similar to what it has been in these cases of urticaria, might well be the means of saving life, when the local application of the drug and other measures had failed.

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[5] Zur Pathologie des Vegetativen Nervensystems, Zeitschr. f. klin. Med., 1909, lxvii, 344.

[6] Bestehen Beziehungen zwischen chromaffinem System und der chronischen Hypertonie des Menschen, Deutsch. Arch. f. klin. Med., 1911, ciii, 397.

[7] The Physiologic Action of Epinephrin on the Bronchi, Jour. Exper. Med., 1912, xvi, 558.

[8] The Influence of Suprarenal Extract upon Absorption and Transudation, Philadelphia, 1904, xxvii, p. 8. Reported in Trans. Assoc. Amer. Phys., 1904.

Another such condition is anaphylaxis, with severe bronchial spasm and edema. From its physiological action on the bronchi and peripheral vessels, epinephrin should theoretically be the most specific of any drug in these cases. That it may relieve the asthma of anaphylaxis, at least temporarily, is well known to clinicians, and its effect on certain urticarias of this type has been shown in this paper. Whether or not it could be made beneficial in every such case if the doses were properly manipulated is a question of some interest. I know of one extreme case of anaphylaxis with dyspnea, but without edema, where epinephrin had no apparent effect, though it is impossible to say what larger and more frequent doses might have done. We know too little, however, of the possible reactions which may in turn follow the primary dilatation produced by the epinephrin to give more than moderate doses in such grave cases, and this point requires further investigation.

The rapidity with which the erythema has faded in my cases suggests the possibility of using epinephrin to differentiate rashes of purely vasomotor origin from those of other types. Hayes[9] suggested its use in diagnosticating serum erythema from the rash of scarlet fever. We have not yet had an opportunity of trying it in a case of scarlet fever, but it is rational to expect that the scarlet rash would fade but little or not at all.

In concluding, I wish to thank Dr. Joseph E. Winters, whose kind permission to work in his wards at the Willard Parker Hospital enabled me to obtain the cases of serum urticaria, and also Dr. R. Hayes for many courtesies extended to me while there.

THE DISSEMINATION AND PREVENTION OF YELLOW FEVER.

By Joseph H. White, M.D.,

SURGEON, UNITED STATES PUBLIC HEALTH SERVICE, NEW ORLEANS, LOUISIANA.

In order to avoid possible misunderstandings, I shall not enter into an argument regarding the relative merits of the observations of Beauperthuy, Knott, and others, but no discussion of

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[9] Personal communication.